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22. (New) A matrix for treatment of restenosis of a blood vessel, comprising a particle made from a polymeric material or a liposome and a combination of an anti-inflammatory agent and anti-thrombogenic substance embedded in the particle.

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23. (New) The matrix of Claim 22, additionally including a polysaccharide coated on the particle.

REMARKS

This is a response to the office action dated January 2, 2002. Claims 1, 3, 4, 8, 10, 12, 13, and 14, have been amended. Claims 5-7, 9, 11and 15 have been canceled, rendering the rejections moot with respect to these claims. Claims 16-23 have been added.

The Examiner has objected to Claim 10 because the word "compirses" was misspelled. Claim 10 has been amended to cure the objection.

Claims 1-15 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Yan (U.S. Patent No. 5,843,172). Yan discloses a metallic stent having pores in which a medication is loaded. With respect to Claim 1, Yan fails to disclose a "device comprising a coating including a first region having a component for reducing or preventing the formation of thrombi and a second region having a component for reducing or preventing infiltration of macrophages in the thrombi, wherein the second region of the coating is positioned beneath the first region," as recited by Claim 1 (emphasis added). Accordingly, Claim 1 is patentably allowable over Yan. Claims 2, 3, and 4 depend from Claim 1 and are therefore allowable for at least the same reason.

With respect to Claims 8 and 10, Yan fails to disclose diclofenac, etodolac, ibuprofen, ketoprofen, ketorolac, nabumetone, naproxen, oxaprozin, clobetasol, diflucortolone, flucinolone, halcinolonide, halobetasol, betamethasone, corticol, cortisone, prednisone, and prednisolone, as recited by the claims. Accordingly, Claim 8 and 10 are allowable over Yan. Claim 12 depends from Claim 10 and is accordingly allowable for at least the same reason.

With respect to Claim 13, Yan fails to "teach a liposome carrying an active component for inhibiting the migration or proliferation of smooth cells wherein the active component inhibits the formation of thrombus and inhibits the infiltration of inflammatory cells in the thrombus." Accordingly, Claim 13 is allowable over Yan. Claim 14 depends form Claim 13 and is therefore allowable for at least the same reason.

Claims 1-15 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Fearnot et al. (U.S. Patent No. 5,609,629). Fearnot et al. teach a stent having a single or multiple bioactive layers containing a therapeutic substance. As indicated by Fearnot et al., the agents used can be heparin as well as anti-inflammatory agents (col 8, line 46 to col. 9, line 21). More particularly, Fearnot et al. teach placing the more soluble agent, e.g., heparin below the less soluble agent, e.g., dexamethasone (col. 10, lines 57-65). To the contrary, Claim 1 recites an opposing configuration of "a first region having a component for reducing or preventing the formation of thrombi and a second region having a component for reducing or preventing infiltration of macrophages in the thrombi, wherein the second region of the coating is positioned beneath the first region."

Accordingly, Claim 1 is patentably allowable over Fearnot et al. Claims 3 and 4 depend from Claim 1 and are therefore patentably allowable for at least the same reason.

With respect to Claims 8 and 10, Fearnot et al. fail to disclose diclofenac, etodolac, ibuprofen, ketoprofen, ketorolac, nabumetone, naproxen, oxaprozin, clobetasol, diflucortolone, flucinolone, halcinolonide, halobetasol, betamethasone, corticol, cortisone, prednisone, and prednisolone, as recited by the claims. Accordingly, Claim 8 and 10 are allowable over Fearnot et al. Claim 12 depends from Claim 10 and is accordingly allowable for at least the same reason.

With respect to Claim 13, Fearnot et al. fail to "teach a liposome carrying an active component for inhibiting the migration or proliferation of smooth cells wherein the active component inhibits the formation of thrombus and inhibits the infiltration of inflammatory cells in the thrombus." Accordingly, Claim 13 is allowable over Fearnot et al. Claim 14 depends form Claim 13 and is therefore allowable for at least the same reason.

Claims 1-5 and 8-11 have been rejected under 35 U.S.C. § 102 (b) as being anticipated by Buscemi et al. (U.S. Patent No. 5,769,883). With respect to Claim 1, Buscemi et al. fail to disclose "a coating including a first region having a component for reducing or preventing the formation of thrombi and a second region having a component for reducing or preventing infiltration of macrophages in the thrombi, wherein the second region of the coating is positioned beneath the first region," as recited by Claim 1. Accordingly, Claim 1 is patentably allowable over Buscemi et al. Claims 2-4 depend

from Claim 1 and are therefore allowable for at least the same reason. As indicated above, Claim 5 has been canceled rendering the rejection moot.

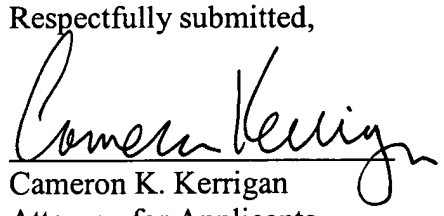
With respect to Claims 8 and 10, Buscemi et al. fail to disclose diclofenac, etodolac, ibuprofen, ketoprofen, ketorolac, nabumetone, naproxen, oxaprozin, clobetasol, diflucortolone, flucinolone, halcinolonide, halobetasol, betamethasone, corticol, cortisone, prednisone, and prednisolone, as recited by the claims. Accordingly, Claim 8 and 10 are allowable over Buscemi et al. Claim 11 has been canceled. Claim 12 depends from Claim 10 and is accordingly allowable for at least the same reason.

CONCLUSION

Applicant believes pending Claims 1-4, 8, 10, and 12-14 and new claims 16-23 are allowable and allowance of the application is hereby solicited. If the Examiner has any questions or concerns, the Examiner is invited to telephone the undersigned attorney at (415) 954-0200.

Date: 6/10/02

Respectfully submitted,



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Version With Markings To Show Changes Made

Specification

Please amend the paragraph on page 10, starting on line 5 as follows:

The desired release profile, which includes parameters such as the rate and duration of release, and the cumulative amount of substance released, may be determined, as described above, based on the characteristics of the substances chosen for the active component. Implementation of the desired release profile can be achieved by varying device design factors in consideration of the solubility *in situ* of the substances. By way of example only, if a therapeutic substance is highly water soluble, the release rate of the substance can be slowed down by converting the substance into a salt form with lower water solubility. Alternatively, the release rate of a highly water soluble substance may be slowed down by choosing a derivative or analog substance with a lower water solubility. The release rate of the substance can also be controlled by varying its solubility in the polymer coating. In general, the lower the solubility of the substance in a polymeric coating, the slower its release rate. Therefore, after an appropriate substance has been chosen, a polymeric coating can be selected in which the substance has the appropriate solubility. The release profile can also be adjusted, for example, by varying the number and thickness of polymer layers, with or without the active [compoenent] component. The interrelation and correlation of these and other design factors for achieving a desired release profile of the therapeutic substances are understood by one of ordinary skill in the art.

Please amend Example 1, on page 15, as follows:

1.5 grams of poly-(n-butyl methacrylate) and 0.5 gram of prednisolone can be dissolved in 100 ml of cyclohexanone and sprayed on a stent using standard small scale spray coating equipment like that available from EFD, Inc. East Providence, RI. The stent[s] can be dried at 75°C, under vacuum for 3 hours. Subsequently, [they] the stent can be overcoated, using the same method[s], with a solution of 0.6% benzalkonium heparin in AMS Techspray (Tech Spray Inc. Amarillo, TX), and dried for 10 minutes at 75°C. The resulting coated stent[s] can have reduced thrombogenicity because of [their] the heparin coating, and can release the anti-inflammatory drug prednisolone for several days.

Please amend Example 4, on Page 16, as follows:

1.5 grams of poly-(n-butyl methacrylate) and 0.5 gram of prednisolone can be dissolved in 100 ml of cyclohexanone and sprayed on a stent using standard small scale spray coating equipment like that available from EFD, Inc. East Providence, RI. The stent[s] can be dried at 75°C, under vacuum for 3 hours. Subsequently, the stent[s] can be overcoated with parylene, and the parylene is functionalized with amine groups by treatment with an ammonia plasma. The over coating and functionalization are standard industrial processes. The amine groups can then be reacted with partially oxidized heparin, binding the heparin to the surface of the parylene by Shiff's base formation, forming a thromboresistant heparin coating.

Please amend Example 5, on page 16, as follows:

1.5 grams of poly-(n-butyl methacrylate) and 0.5 gram of prednisolone and 0.5 gram of acetyl salicylic acid can be dissolved in 100 ml of cyclohexanone/methanol (50/50) and sprayed on a stent using standard small scale spray coating equipment like that available from EFD, Inc. East Providence, RI. The stent[s] can be dried at 75°C, under vacuum for 3 hours. The prednisolone can provide long term anti-inflammatory action, while aspirin can provide both short term anti-inflammatory action as well as thromboresistance due to its anti-platelet activity.

Please amend Example 7, on page 17, as follows:

1.5 gram of poly-(n-butyl methacrylate) and 0.5 gram of prednisolone and 0.5 gram of benzalkonium heparin can be dissolved in 100 ml of cyclohexanone/Techspray (10/90) and sprayed on a stent using standard small scale spray coating equipment like that available from EFD, Inc. East Providence, RI. The stent[s] can be dried at 75°C, under vacuum for 3 hours.

Please amend Example 8, on Page 17, as follows:

1.5 gram of poly-(n-butyl methacrylate) and 0.5 gram[s] of rapamycin are dissolved in 100 ml of cyclohexanone/methanol (50/50) and can be sprayed on a stent using standard small scale spray coating equipment like that available from EFD, Inc. East Providence, RI. The stent[s] can be dried at 75°C, under vacuum for 3 hours. Subsequently, the stent[s] can be overcoated, using the same method[s], with a solution of 0.6% benzalkonium heparin in AMS Techspray (Tech Spray Inc. Amarillo, TX), and dried for 10 minutes at 75°C. The resulting coated stent[s] can have reduced

thrombogenicity because of [their] the heparin coating, and can release rapamycin for several days. Rapamycin, in addition to being a potent immune suppressor, also has anti-inflammatory activity.

Please amend Example 9, on page 17, as follows:

1.5 grams of poly-(ethylene vinyl alcohol-co ethylene) (EVAL or EVOH) and 0.5 gram of prednisolone can be dissolved in 100 ml of dimethylsulfoxide (DMSO) and sprayed on a stent using standard small scale spray coating equipment like that available from EFD, Inc. East Providence, RI. The stent[s] can be dried at 75°C, under vacuum for 12 hours. Subsequently, the stent[s] can be overcoated, using the same method[s], with a solution of 0.6% benzalkonium heparin in AMS Techspray (Tech Spray Inc. Amarillo, TX), and dried for 10 minutes at 75°C. The resulting coated stent[s] can have reduced thrombogenicity because of [their] the heparin coating, and can release the anti-inflammatory drug prednisolone for several days.

Please amend Example 10, on page 18, as follows:

1.5 gram of poly-(n-butyl methacrylate) and 0.5 gram of prednisolone can be dissolved in 100 ml of cyclohexanone and sprayed on a stent using standard small scale spray coating equipment like that available from EFD, Inc. East Providence, RI. The stent[s] can be dried at 75°C, under vacuum for 3 hours. Subsequently, the system is overcoated with a thin layer of PTFE, using a commercially available method (such as that described by Advanced Surface Engineering, Inc, Eldersburg, MD). The low surface

energy of the teflon coating can prevent protein deposition, and subsequent thrombus accumulation, while the prednisolone can provide the anti-inflammatory component.

CLAIMS

Please amend the claims as follows. The italicized claims have not been amended but are provided for the Examiner's convenience.

1. (Amended) A method for inhibiting restenosis of a blood vessel, comprising [the acts of]:

> [a. providing a device carrying an active component, the active component comprises at least one anti-thrombotic substance and at least one anti-inflammatory substance; and]
>
> [b.] implanting [the] a device into the blood vessel of a patient, the device comprising a coating including a first region having a component for reducing or preventing the formation of thrombi and a second region having a component for reducing or preventing infiltration of macrophages in the thrombi, wherein the second region of the coating is positioned beneath the first region. [to inhibit restensosis of the blood vessel.]

2. The method of Claim 1, wherein the device is selected from a group of balloon-expandable stents, self-expandable stents, and grafts.

3. (Amended) The method of Claim 1, wherein

the [anti-thrombotic substance] component for reducing or preventing the formation of thrombi is selected from a group of heparin, sodium heparin, low molecular weight heparin, hirudin, argatroban, forskolin, vapiprost, prostacyclin and prostacyclin analogs, D-phe-pro-arg-chloromethylketone, dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor antibody, and recombinant hirudin; and

the [anti-inflamatory substance] component for reducing or preventing the infiltration of macrophages in the thrombi is selected from a group of aspirin, diclofenac, etodolac, ibuprofen, ketoprofen, ketorolac, nabumetone, naproxen, oxaprozin, clobetasol, diflucortolone, flucinolone, halcinolonide, halobetasol, dexamethasone, betamethasone, corticol, cortisone, prednisone, and prednisolone.

4. (Amended) The method of Claim 1, wherein the [device is coated with] coating includes an ethylene vinyl alcohol copolymer or a poly(n-butyl methacrylate) polymer. [and the active component is contained in the ethylene vinyl alcohol copolymer.]

5.-7. Please Cancel Claims 5-7.

8. (Amended) A stent comprising pores formed in the surface wherein the sent is made from an anti-thrombogenic material and wherein the pores contain an anti-inflammatory substance, the anti-inflammatory substance being selected from a group consisting of diclofenac, etodolac, ibuprofen, ketoprofen, ketorolac, nabumetone, naproxen, oxaprozin, clobetasol, diflucortolone, flucinolone, halcinolonide, halobetasol, betamethasone, corticol, cortisone, prednisone, and prednisolone.

9. Please Cancel Claim 9 without prejudice.

10. (Amended) A stent for inhibiting restenosis of a mammalian blood vessel, comprising a generally tubular structure [and] carrying an active component, wherein the active component[s] [compirses] comprises an anti-thrombogenic substance selected from a group of heparin, sodium heparin, low molecular weight heparin, hirudin, argatroban, forskolin, vapiprost, prostacyclin and prostacyclin analogs, D-phe-pro-arg-chloromethylketone, dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor antibody, and recombinant hirudin and an anti-inflammatory substance selected from a group of diclofenac, etodolac, ibuprofen, ketoprofen, ketorolac, nabumetone, naproxen, oxaprozin, clobetasol, diflucortolone, flucinolone, halcinolonide, halobetasol, betamethasone, corticol, cortisone, prednisone, and prednisolone.

11. Please cancel Claim 11 without prejudice.

12. (Amended) The stent of Claim 10, wherein the stent has an ethylene vinyl alcohol or a poly(n-butyl methacrylate) coating which contains the active component.

13. (Amended) A [polymeric] matrix comprising a liposome carrying an active component for inhibiting the migration or proliferation of smooth cells wherein the active component inhibits the formation of thrombus and inhibits the infiltration of inflammatory cells in the thrombus.

14. (Amended) The [polymeric] matrix of Claim 13, [wherein the polymer is a liposome] additionally including a polysaccharide for inhibiting the liposme's uptake by the inflammatory cells.

15. Please cancel claim 15 without prejudice.

Please add the following new claims:

-- 16. The matrix of Claim 13, wherein the matrix is in the form of a particle.

17. The stent of Claim 8, wherein the anti-thrombogenic material reduces or prevents the formation of thrombi.

18. A stent comprising a coating having a first region and a second region disposed beneath the first region, the first region having a substance for the treatment of thrombus formation and the second region having a steroidal or non-steroidal anti-inflammatory substance.

19. A stent comprising a first layer containing an anti-inflammatory drug and a second layer disposed over the first layer, wherein the second layer reduces or prevents the formation or accumulation of thrombi on the stent.

20. The stent of Claim 19, wherein the second layer is made of a material comprising polytetrafluoroethylene.

21. A method of treatment of restenosis of a blood vessel, comprising injecting a polymeric composition in a liquid form in a region of the blood vessel in need of treatment, the composition including a first agent capable or reducing or preventing formation of thrombus and a second agent having anti-inflammatory characteristics; and causing the polymeric composition to solidify.

22. A matrix for treatment of restenosis of a blood vessel, comprising a particle made from a polymeric material or a liposome and a combination of an anti-inflammatory agent and anti-thrombogenic substance embedded in the particle.

23. The matrix of Claim 22, additionally including a polysaccharide coated on the particle.--